REMARKS

Claims 1-53 have been cancelled without prejudice.

New claims 54-70 have been added.

Figure 5 has been replaced with replacement Figure 5 to correct the spelling of "aldehyde".

The sequence listing filed July 12, 2001 has been replaced with a new sequence listing on compact disc containing the statement: "The contents of this sequence listing information recorded in computer readable form is identical to the written (On paper or compact disc) sequence listing and contains no new matter."

The paragraph in the specification on page 4 line 23 through page 5 line 1 has been replaced to correct the spelling of "limited".

The paragraph in the specification on page 51 line 28 through page 52 line 15 has been replaced to insert "SEQ ID NO.: 1".

Applicant believes that none of the amendments above add new matter to the specification.

PATENTABILITY ARGUMENTS

A. The 35 U.S.C. §112 Second Paragraph Rejections Should Be Withdrawn Because It Has Been Traversed.

In item 5 the Examiner rejects claims 1, 2, 22-30 and 40-44 under 35 U.S.C §112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention. More particularly, the Examiner rejects claim 1 because he feels that the term "a derivative thereof" on page 57 line 4 is unclear as to what degree of structural and/or functional similarity to a compound of formula I is required to be considered "a derivative thereof". In addition, the Examiner requests that Applicant replace the word "among" with the phrase "consisting of". The Examiner further rejects claim 1 because it recites R^{11} when no R^{11} appears as an element of the claim. Finally, the examiner rejects claim 29 stating that there is no antecedent basis for the phrase "the amino moiety or thiol moiety".

Applicant has cancelled claims 1, 2, 22-30 and 40-44, consequently, these rejections are moot. In view of this Applicant respectfully requests that the Examiner remove these rejections.

B. The 35 U.S.C §102(b) Rejection Should Be Withdrawn Because The Claimed Invention Is Not Anticipated by the Cited Reference

In item 8, the Examiner rejects claims 1, 2, 22, 25 and 29 under 35 U.S.C. §102(b) as being anticipated by WO patent application 93/14779 ("779"). The Examiner states that 779 teaches a compound at page 22, Example 5, which anticipates Applicant's compound of formula I in which B is a carboxyl group; R is a cycloalkylene group combined with a $C(R^{10})_2$ group where R^{10} is hydrogen; A is -NH(C=O)-; and X is trifluoroacetate. The Examiner further states that the compound of Example 5 is reacted with an arginine derivative which is a synthetic biological molecule, and the product is then conjugated to an amino group of a solid phase resin in Example 7. Applicant respectfully disagrees.

To maintain a rejection under 35 U.S.C. 102 (b) the reference must teach each and every aspect of the claimed invention. No where in Applicant's invention does he teach the compound of formula I in which B is a carboxyl group. Consequently a rejection based on 35 U.S.C. §102 (b) cannot be maintained. In addition, Applicant has cancelled claims 1, 2, 22, 25 and 29, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

In item 10 the Examiner rejects claims 1, 2, 22, 23 and 25-27 under 35 U.S.C. §102(b) as being anticipated by Schwartz *et al.* Patent no.: 5,206,370 ("370"). The Examiner states that 370 teach succinimidyl 4-hydrazinobenzoate hydrochloride, which is reacted with amino groups present in IgG to form a conjugate. The succinimidyl 4-hydrazinobenzoate hydrochloride is deemed by the Examiner to be a derivative of Applicant's claimed compound of formula I. Applicant respectfully disagrees.

To maintain a rejection under 35 U.S.C. 102 (b) the reference must teach each and every aspect of the claimed invention. No where in Applicant's invention does he teach the compound of formula I in which R is a aromatic moiety such as a benzyl group. In fact Applicant specifically states the R is a aliphatic divalent group. Consequently a rejection based on 35 U.S.C. §102 (b) cannot be maintained. In addition, Applicant has cancelled claims 1, 2, 22, 23 and 25-27, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

In item 11 the Examiner ejects claims 1, 2, 22 and 24-26 under 35 U.S.C. §102(b) as being anticipated by Sytkowski patent no.: 5,919,758 ("758"). The Examiner states that 758 teaches 4-(N-maleimidomethyl)cyclohexane-1-carboxyl-hydrazide-HCl which is used to crosslink erythropoietin molecules. More specifically the examiner states that 758 anticipates Applicant's formula I in which B is maleimido group, R is a cycloalkylene group combined with a C(L) group in which L is O; A is a direct bond to R and X is Cl.

Applicant has cancelled claims 1, 2, 22, and 24-26 consequently this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

In item 12 the Examiner rejects claims 1, 2, 25-27, 30, 41 and 44 as being anticipated by Sivam *et al.* patent no.: 5,521,290 ("290"). The Examiner states that 290 teaches derivatizing a monoclonal antibody with sulfhydryl groups, reacting a hydrazide-containing bifunctional linker of formula I with the derivatized monoclonal antibody, and then reacting the monoclonal antibody hydrazide with ricin A which has been oxidized to form aldehyde groups on its oligosaccharide moieties.

Applicant has cancelled claims 1, 2, 25-27, 30, 41 and 44, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

In item 14 the Examiner rejects claims 1, 2, 25, 30, 41, 42 and 44 as being anticipated by Berninger *et al.* patent no.: 5,856,571 ("571"). The Examiner states that 571 teach reacting a first hydrazide-containing linker having the structure at column 5, lines 22-24, with biotin to form a hydrazide-containing biotin conjugate. The conjugate is then reacted with an antibody, which has been subjected to periodate oxidation so as to form aldehyde groups on its oligosaccharide substitutents. The Examiner further states with respect to claims 25, 30, 41 42 and 44 that 571 does not teach its hydrazide linker in salt form but is none the less deemed to be a derivative of Applicant's claimed compound of formula I. Applicant respectfully disagrees.

Applicant has cancelled claims 1, 2, 25, 30, 41, 42 and 44, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

In item 16 the Examiner rejects claims 1, 2, 22, 25, 26 and 44 as being anticipated by Heindel *et al.* Article (Bioconj. Chem. 2:427-430). The Examiner states that Heindel *et al.* teach a heterobifunctional linker which corresponds to Applicant's compound of formula I in which B is a thiol reactive moiety, R is a combination of a $C(R^{10})_2$ group and C(L) group where L is O; A is a direct bond to R: and X is Cl. He further states that the heterobifunctional crrosslinker is used to bind a monoclonal antibody to a polyaldehyde dextran by first reacting the linker with the polyaldehyde dextran and then reacting the monoclonal antibody.

Applicant has cancelled claims 1, 2, 22, 25, 26 and 44, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

In item 17 the Examiner has rejected claims 1, 2, 22, 25-27 and 44 as being anticipated by Zara *et al.* Article (Analytical Biochemistry 194:156-162). The Examiner states that Zara *et al.* teach a heterobifunctional crosslinker TPCH which corresponds to Applicant's compound of formula I in which B is a thiol reactive moiety; R is a combination of

C(R10)2 groups and C(L) group where L is O; A is a direct bond to R; and X is Cl. The Examiner continues stating that the heterobifunctional crosslinker is used first to modify a periodate-treated antibody and then to react a pyridyl disulfide-derivatized barley toxin with the modified antibody.

Applicant has cancelled claims 1, 2, 22, 25-27 and 44, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

C. The 35 U.S.C §102(e) Rejection Should Be Withdrawn Because The Claimed Invention Is Not Anticipated by the Cited Reference

In item 15 the Examiner has rejected claims 25, 26, 28, 40 and 43 under 35 U.S.C. 102(e) as being anticipated by Whelihan U.S. Patent no.: 6,238,860 ("860"). More specifically, the Examiner states that Whelihan teaches polypeptides which are synthesized with a Glu-Gly-Gly-Gly-Ser spacer sequence, modified with a hydrazide functionality, and then immobilized on an aldehyde-functional methacrylate resin support. The examiner further states that the spacer of 860 corresponds to Applicant's B-R-A groups of formula I: the carboxyl group of the Glu residue corresponds to B which is reactive with the amino group; the remainder of the spacer sequence corresponds to R which is a combination of $C(R^{10})_2$, $N(R^{10})$ and C(L) groups where L is O; and A is a direct bond to R .

Applicant has cancelled claims 25, 26, 28, 40 and 43, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

D. The 35 U.S.C §103(a) Rejection Should Be Withdrawn Because The Claimed Invention Is Not Obvious in view of the Cited References

In order to maintain a rejection under 35 U.S.C. 103(a) their must be some motivation to combine the teachings of the cited references, there must a reasonable expectation of success when combining the teachings of the references and the references must teach or suggest all of the claim limitations.

In item 9 the Examiner rejects claims 1, 2, 22, 25 and 29 and 21 under 35 U.S.C. §103(a) as being unpatentable over 779 in view of Abrams et al. U.S. patent no.: 5,679,778 ("778") and Ashkenazi *et al.* U.S. patent no. 5,329,028 ("028"). More specifically, the Examiner states that 779 differs from Applicant's elected species in that compound 5 comprises a trifluoroacetate salt rather than a hydrochloride salt. Patent 778 teaches bifunctional linkers having a hydrazide present in acid addition salt form. Patent 028

teaches bifunctional linkers in which both hydrazide and maleimido functional groups are present wherein the hydrazide group is present in the form of hydrachloride. The Examiner then states that the substitution of one known equivalent for another is prima facie obvious. Applicant respectfully disagrees.

As stated previously no where in Applicant's invention does he teach the compound of formula I in which B is a carboxyl group as suggested by the Examiner. Consequently, a rejection based on 35 U.S.C. §103 (a) cannot be maintained because the combined references do not teach all of Applicant's claimed limitations. However, Applicant has cancelled claims 1, 2, 22, 25 and 29, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

In item 13 the Examiner rejects claims 1, 2, 25-27, 30, 41 and 44 under 35 U.S.C. §103(a) as being unpatentable over 290 in view 778 and 028. More specifically, the Examiner states that 290 do not teach their bifunctional linker in the salt form and patent 778 teaches bifunctional linkers in which a hydrazine group is present in the acid addition salt form and patent 028 teaches bifunctional linker having both a hydrazide and a maleimide functional groups present in the form of a hydrochloride. The Examiner then states that the substitution of one known equivalent for another is prima facie obvious.

Applicant has cancelled claims 1, 2, 25-27, 30, 41 and 44, consequently, this rejection is moot. In view of this Applicant respectfully requests that the Examiner remove this rejection.

CONCLUSION

In view of the above arguments Applicant has demonstrated that the invention as claimed satisfies the statutory requirements for patentability. Applicant respectfully requests that the Examiner issue an allowance of the claims.

Respectfully submitted,

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